

### **Remarks/Arguments**

Prior to the present amendment, claims 1-46 were pending in this application. Non-elected claim 26 has been canceled, claim 42 has been amended. The amendments are fully supported by the specification as originally filed, including the original claims, and do not add new matter. The amendments, including the cancellation of claim 26, were made without prejudice or disclaimer. Applicants specifically reserve the right to pursue any deleted subject matter in one or more continuing applications.

### ***Election/Restriction***

Applicants were requested to elect, for examination purposes, one of the following groups: Group I (claims 1-25, 27-45), and Group II (claim 26). It is noted that the restriction requirement fails to include claim 46. Since claim 46 depends from claim 45, it should have been included in Group I. Accordingly, the election of the claims of Group I, claims 1-25, and 27-46, is hereby confirmed. Non-elected claim 26 has been canceled.

### ***Claims Rejections – 35 USC § 103***

Claims 1-25, and 27-45 were rejected as allegedly obvious over Basey et al. (WO 99/57134) and Houtchens et al. (WO 00/02921). According to the rejection, “Basey et al. teaches the separation of peptides using anion/cation exchange resin chromatography,” and “gives details of the material used in the stationary phase and the solvent system used for the chromatography.” While the Examiner acknowledges that the Basey et al. reference “does not teach the continuous increase of the concentration of the salt in the elution system,” she notes that “Halenback et al. [sic!] also teaches the separation of protein and related products using anion/cation exchange chromatography.” In further support of the rejection, the Examiner adds that the latter reference “teaches the use of continuous increase of the salt percentage in the solvent system to get final product in the pure form.”

The rejection is confusing and contains several material errors.

First of all, claim 46 is not included in the rejection, which is the sole rejection in this case. Secondly, the secondary reference is first identified in the rejection as Houtchens et al. (WO 00/02921), and this is the reference listed in the Notice of References Cited. Confusingly, in the explanation of the rejection, the teaching of Basey et al. is combined with “Halenback et

al.” Since a “Halenback et al.” reference is not identified in the Office Action, Applicants will assume that it is cited in error, and it has been the Examiner’s intention to base the present rejection on the combination of Basey et al. and Houtchens et al. Should this not be the case, the Examiner is respectfully requested to identify the Halenback et al. reference, and explain its relevance in a new, non-final Office Action.

Basey et al. teaches the purification of polypeptides (including antibodies) by ion exchange chromatography. As the Examiner correctly notes, Basey et al. do not teach the use of an increasing salt concentration in the solvent system used in the purification scheme. Contrary to the Examiner’s assertion, the secondary reference, Houtchens et al. does not concern the separation of proteins in and related products in general, by anion/cation chromatography. Houtchens et al. concerns the purification of a particular protein, hemoglobin, by anion exchange chromatography. Similarly, the statement that this reference “teaches the use of continuous increase of the salt percentage in the solvent system” appears to be in error. As stated on page, lines 19-20, the method of Houtchens et al. “is characterized in the use of a pH gradient to elute the hemoglobin component.” (Emphasis added.)

*The references cannot be properly combined*

Since the teaching of Houtchens et al. is specific to the purification of a particular protein, hemoglobin, the combination of Basey et al. (concerning protein purification by ion exchange chromatography in general) is legally and scientifically improper. In the absence of any disclosure, teaching or suggestion in Houtchens et al. that its purification scheme would be applicable to the purification of proteins other than hemoglobin, there is no basis for the purported combination, other than a legally impermissible attempt of hindsight reconstruction of the present invention. Indeed, since the purpose of Houtchens et al. is to produce a purified hemoglobin product substantially free of other blood protein components (see, e.g. page 4, lines 16-19), its purification scheme specifically targets the elimination of such undesired blood protein components.

*Even if the cited references could be properly combined, they would not make obvious the claimed invention.*

Claims 1-25 of the present application recite a method of protein purification using ion exchange chromatography in which the salt concentration increases from the equilibration buffer to the initial salt concentration of the wash buffer, and then again throughout the washing step.

Neither Basey et al. nor Houtchens et al. teaches the use of a salt gradient during protein purification, therefore, their combination does not make obvious the invention claimed in claims 1-25.

Basey et al. teaches a change of conductivity or pH from a loading buffer through an intermediate buffer to a wash buffer, which has some relevance to claims 27 and 42, and the claims dependent thereon. However, while in the case of the present invention the conductivity changes in one (increasing) direction, Basey et al. teach that the conductivity (or pH) changes from the loading buffer to the intermediate buffer and from the intermediate buffer to the wash buffer, respectively, are in opposite directions, i.e. if the conductivity (or pH) of the intermediate buffer is higher than the conductivity (or pH) of the loading buffer, then the conductivity (or pH) of the wash buffer will be lower than the conductivity (or pH) of the intermediate buffer, and vice versa. Houtchens et al. does not teach a change in conductivity, rather, as stated before, relies on a pH gradient in its purification scheme. It is noted that there is no direct relationship between pH and conductivity. The conductivity of solutions depends on the concentration of ions in solution, their ability to dissociate (if positive and negative ions never separate, current will not flow), their charges, and their speed of diffusion (small, light ions will travel faster than large, heavy ones). The pH specifically tells the concentration of one particular ion,  $H^+$ . This by itself does not uniquely specify the conductivity of the solution, because it does not tell anything about the presence of other ions that may affect the electrical conductivity, or about the speed of diffusion. Accordingly, the combination of Basey et al. and Houtchens et al. does not make obvious the invention claimed in claims 27-46 either.

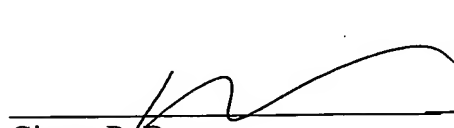
In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

All claims pending in this application are believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (referencing Attorney's Docket No. 39766-0113A).

Respectfully submitted,

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